REMARKS

I. Request for an interview

Applicant would like to request an interview with the Examiner before the issuance of the next Office Action in order to discuss the instant rejections. Applicant respectfully requests that the Examiner call the undersigned, Arthur S. Garrett at (202) 408-4091 or Carlos M. Tellez at (202) 408-4123 at the Examiner's convenience to discuss the possibility of scheduling the aforementioned interview.

II. Status of the claims

Claims 1-6 and 8-22 are currently pending. Solely to facilitate prosecution and without prejudice or disclaimer, Applicant has amended claims 1, 4-6, 21, and 22 to indicate that the label to be detected is associated with the ligand or the IgE antibody. Support for this amendment may be found in the specification at pages 7-9.

Applicant acknowledges the Office's withdrawal of the previous rejection of the claims under 35 U.S.C. § 112, both first and second paragraphs, the previous rejection of claims under 35 U.S.C. § 102, and the previous rejection of claim 15 under 35 U.S.C. § 103 over U.S. Pat. 6,087,188, "*Johansen*;" in view of U.S. Pat. 6,034,066, "*Johnson*;" and U.S. Pat. 6,060,326, "*Frank 2*."

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 1, 6, 8-16, 21, and 22 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The Office argues that it is unclear to which components in the mixture the label recited in the rejected claims is attached. Applicants respectfully traverse.

The skilled artisan analyzing claims 1, 6, 8-16, 21, and 22 in light of the specification (M.P.E.P. § 2173.02) would understand that the label is associated with the ligand or the IgE antibody. Specification at p. 7-9. However, solely to expedite prosecution and without prejudice or disclaimer, Applicant has amended independent claims 1, 4-6, 21, and 22 to indicate that the label is associated with the ligand or the IgE antibody. As mentioned previously, support for this amendment may be found in the specification at pages 7-9. Because the ligand and the IgE antibody are present in steps (a)-(c), for example in claim 1, the label can be added to the complexes formed in any one of those steps.

In light of the above arguments and amendments, the Office's rejection is now moot and Applicant respectfully requests that the rejection be withdrawn.

IV. Rejections Under 35 U.S.C. § 103

A. *Johansen* in view of *Johnson* and *Frank 2*

The Office maintained the rejection of claims 1-5, 8-14, 16, 21, and 22 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Pat. 6,087,188, "*Johansen*;" in view of U.S. Pat. 6,034,066, "*Johnson*;" and U.S. Pat. 6,060,326, "*Frank 2*." According to the Office, *Johansen* teaches a method of detecting an antibody using a ligand bound to biotin; an antibody to the antibody to be detected; and a chemiluminescent acridinium compound bound to avidin. According to the Office, *Johnson* allegedly teaches the role of CD23 in regulating the immune response, such as IgE responses. The Office alleges that *Frank 2* teaches a method for detecting IgE antibodies using a human Fc epsilon receptor. The Office argues that it would have been obvious to one of ordinary skill in

the art to use the IgE receptors of *Johnson* and *Frank 2* to measure IgE according to the method of *Johansen* alleging that CD23 and FcεRI are more specific to IgE than the anti-IgE antibody used in *Johansen*. In addition, with regard to claim 16, the Office believes it would have been obvious to use enough ligand molecules to optimize binding of all the IgE molecules in the sample. Applicant respectfully traverses.

In contrast to the cited references, which, according to the Office may teach avoidance of cross-reactivity from other immunoglobulins (*see* Frank 2, at col. 1, lines 36-41), the present invention "simulates any interference from other immunoglobulins, as well as any other potentially interfering component, present in the sample." Specification at p. 5, lines 22-25.

To that end, the specification shows that when the methods of the invention (employing an IgE receptor) are used to measure IgE in individuals who have been subjected to Specific Allergy Vaccination (SAV), the amount of IgE detected is lower than the total amount of IgE detected in the same sample with a commercial kit, which uses an anti-IgE antibody instead of an IgE receptor. *See* Example 2 of the specification. This result suggests that the amount of IgE measured with the methods of the invention more closely resembles the physiological activity of IgE *in vivo*, where the presence of other allergens inhibits the binding of IgE to an IgE receptor. *Id.* The importance of the methods of the invention is evident in subjects receiving SAV treatment, which "results in an inhibition or reduction of the binding of IgE to IgE receptors, [and where] the relevant *in vivo* level of IgE gives a much more precise measure of the severity of the allergic disease." Specification at p. 6, lines 18-27.

None of the references cited by the Office recognizes the above difference between total IgE and physiologically active IgE. Applicant notes that none of the cited references, alone or in combination, discloses or even suggests a method of detecting IgE that "allows the binding reactions between the various reactants to be carried out in more *in vivo* like conditions so as to give an IgE measurement that reflects the ability of IgE to exert its effector functions through binding to its receptor rather than measuring the presence of IgE in a sample." Specification at p. 3, lines 22-30, underlining added. Clearly, the combination of these references fails to render obvious the present invention.

Applicant now addresses this rejection in detail.

The Office is respectfully reminded that in order to prove a *prima facie* case of obviousness, the Office needs to establish, *inter alia*, that: a) the skilled artisan had motivation to combine the teachings of the prior art; and b) the modification would have had a reasonable likelihood of success in light of the prior art. M.P.E.P. § 2143.

i. *Frank 2* provides no motivation to combine *Johansen* and *Frank 2*

The Office seems to cite *Frank 2* and *Johnson* solely for the proposition that the IgE receptors disclosed therein can be used in place of anti-IgE antibodies in the method of *Johansen*. The Office admits that *Johansen* does not teach IgE receptors but argues that the skilled artisan would have been motivated to use IgE receptors in the method of *Johansen* because *Frank 2* discloses that the IgE receptor FcεRI can bind to IgE with less isotype cross-reactivity and more sensitivity than the original anti-IgE antibodies used in *Johansen*.

The Office, however, has provided no explanation for why the skilled artisan would be motivated to pick and choose particular features from the two methods—at the expense of leaving other features out—and then combining such selected features in order to arrive at the present invention. Applicant submit that the Office has failed to consider the teachings of *Johansen* and *Frank 2* as a whole, as required by M.P.E.P. §2141.03.

Both *Johansen* and *Frank 2* teach methods to detect IgE. Each does so using a protocol different from the other and again different from the Applicant. For example, *Johansen* uses anti-IgE antibodies to bind the IgE molecules to be measured, while *Frank 2* uses an IgE receptor to bind the IgE molecules. *See Johansen* at col. 3, lines 33-51; *Frank 2* at col. 1, lines 49-58. Furthermore, *Johansen* mixes an IgE-binding ligand with the test sample (IgE) in the presence of the anti-IgE antibody. *Johansen* at col. 3, lines 33-51. *Frank 2*, on the other hand, either omits the step of mixing an IgE-binding ligand with IgE or places it after the IgE is bound to the IgE receptor. *See, e.g., Frank 2* at col. 1, lines 49-58; col. 7, line 21 to col. 13, line 44.

Having found *Johansen* and *Frank 2*, the skilled artisan—faced with the problem of finding a method to detect IgE—would select the best of the two methods. If one follows the Office's premise that a method that uses IgE receptors instead of anti-IgE antibodies is better because IgE receptors are more sensitive and specific than anti-IgE antibodies, then the skilled artisan would choose to use *Frank 2's* method, *in its entirety*. In other words, the Office has provided no motivation for the skilled artisan to use the IgE receptor of *Frank 2* in *Johansen* instead of simply following the teachings of *Frank 2*. Neither *Johansen* nor *Frank 2* suggest that following a given step from one of

the two methods would provide a particular benefit over following the steps from the other method. That is, there is no teaching or suggestion that mixing and matching features from both methods would be more beneficial *than simply following the apparently superior method of Frank 2*. On the contrary, given that the methods disclosed in *Johansen* and *Frank 2* involve different steps and the presence of different reagents in solution at different times, the skilled artisan would be persuaded to simply follow the teachings of the method that provides an overall advantage over the other, *i.e., Frank 2*.

Johnson does not cure the deficiencies of *Frank 2* and *Johansen*. *Johnson* discusses a protease that can digest CD23 and a novel inhibitor of that protease. *Johnson* does not discuss FcεRI. More importantly, *Johnson* is silent regarding the use of an IgE receptor in a method for detecting an IgE antibody and does not even mention methods for detecting IgE at all. Accordingly, *Johnson* cannot provide the requisite motivation to develop a method for detecting an IgE antibody comprising the use of an IgE receptor as instantly claimed.

Regardless, even had one skilled in the art stumbled onto the best combination from the references without motivation, they still would not have the method disclosed in the present invention for the reasons stated above. For example, the combination of the cited references encourages avoiding cross-reactivity between different immunoglobulins. *Frank 2* at col. 1, lines 35-41. In contrast, the instant invention accounts and "simulates any interference from other immunoglobulins, as well as any other interfering component present in the sample." Specification at p. 5, lines 22-28.

See also the next section for a discussion regarding the lack of expectation of success when combining the references cited by the Office.

For at least these reasons, the Office has not met its burden of proving a *prima facie* case of obviousness and Applicant respectfully requests that this rejection be withdrawn.

ii. The skilled artisan had no expectation of success when using the IgE receptors from *Frank 2* or *Johnson* in the method of *Johansen*

Moreover, even assuming, *arguendo*, that there was motivation to combine the teachings of *Frank 2* and *Johansen*, the Office has provided no evidence to suggest that the combination would have had any expectation of success.

As mentioned previously, the methods for detecting IgE disclosed in *Frank 2* and *Johansen* involve different steps and different reagents. For example, *Johansen* always mixes the test sample with both an IgE-binding ligand and an anti-IgE binding antibody. *Johansen* at col. 1, lines 30-51; Examples 1-8. In contrast, the preferred method in *Frank 2* involves direct binding of an IgE receptor and IgE in the absence of an IgE-binding ligand. *Frank 2* at col. 10, lines 36-60. Indeed, none of *Frank 2's* working examples discloses the addition of an IgE-binding ligand to the mixture. *See* Examples 1-5 in *Frank 2*.

Moreover, in *Johansen's* working examples, the binding reactions take place in a suspension of paramagnetic particles and reagents in the absence of solid supports. On the other hand, the binding reactions in the working examples of *Frank 2* take place between a solid support and a reagent-containing solution. These remarks indicate that the conditions under which the IgE receptor in *Frank 2* and the anti-IgE antibody in

Johansen are used to measure IgE concentrations are different and involve different binding environments (*e.g.*, solid supports vs. suspension of particles). The Office has provided no evidence to suggest that these differences would not be significant and would not affect the performance of the IgE receptor disclosed in *Frank 2* when used under the experimental conditions of *Johansen*.

Given that the sequence in which binding reagents (*i.e.*, IgE, IgE-binding ligand, anti-IgE antibody, or IgE receptor) react with one another affects the outcome of the binding reaction (*see, e.g.*, specification at p. 5, lines 6-20), it is unclear from the experimental results disclosed in *Frank 2* and *Johansen* whether the performance of an IgE receptor, which is preferably used in the absence of an IgE-binding ligand (*Frank 2* at col. 10, lines 36-60), would be unaffected when said receptor is used in the presence of said IgE-binding ligand.

The Office has not provided evidence to suggest that there was an expectation that one could extrapolate the use of a reagent (FcεRI receptor) utilized under a particular set of conditions (*Frank 2*) and expect it to work as a replacement of another reagent (anti-IgE antibody) under a different set of conditions (*Johansen*). This is particularly true when the primary physiological function of an antibody and a receptor is different. *See, e.g.*, B. Alberts et al., *The Molecular Biology of the Cell*, Glossary at 2, 19, 20 (3rd Ed. 1983) enclosed for the Office's convenience.

As pointed out previously, *Johnson*, does not even mention the use of an IgE receptor in a method of detecting an IgE antibody. Therefore, *Johnson* cannot cure the deficiencies of *Johansen* and *Frank 2* regarding an expectation of success in using IgE

receptors in place of anti-IgE antibodies as instantly claimed. In light of these remarks, Applicant respectfully requests that the rejection be withdrawn.

B. *Johansen* in view of *Frank 2* and *Arnold*

The Office rejected claims 6 and 17-20 under 35 U.S.C. § 103(a) as allegedly obvious in view of *Johansen* and in further view of *Frank 2* and U.S. Patent 6,004,745 "*Arnold*". According to the Office, "it would have been obvious to one of ordinary skilled in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold Jr. using the reagents in the method of Johansen modified by Frank." Office Action dated December 16, 2003, at p. 7 last ¶.

This rejection assumes that prior to applying the teachings of *Arnold*, the skilled artisan would have combined the teachings of *Johansen* and *Frank 2* in order to arrive at a method for detecting IgE using an IgE receptor. As mentioned in the previous section, the Office has failed to provide the motivation and expectation of success required to prove a *prima facie* case of obviousness when combining *Johansen* and *Frank 2*. For at least this reason, Applicant respectfully requests that this rejection be withdrawn.

Moreover, the addition of *Arnold* fails to provide the necessary motivation that was lacking as discussed above. According to the Office, *Arnold* discusses a "typical" sandwich immunoassay wherein an antigen is sandwiched between an immobilized antibody and a labeled antibody. Office Action at p. 7, ¶ 4. Applicant understands that the Office suggests that the immobilized antibody be replaced with the IgE receptor of *Frank 2* in order to arrive at the present invention. Office Action at p. 7, ¶ 5. However, with respect to claims 17-19, the Office has not explained why the skilled artisan would

replace *only* the immobilized antibody with an IgE receptor to arrive at the invention instead of replacing both antibodies, which, as alleged by the Office, would provide more specificity and sensitivity to the method. Office Action at p. 8, last ¶. There is no teaching or suggestion anywhere in the cited references that such a single replacement would offer any particular advantage over a double replacement. To cure this lack of motivation, the Office has applied impermissible hindsight when combining the cited references. M.P.E.P. §2141. Again, the Office has not established a prima facie case of obviousness.

Moreover, the combination of *Johansen*, *Frank 2*, and *Arnold* fails to meet all of the limitations of the rejected claims as required by M.P.E.P. § 2143.03. For example, with respect to claim 20, the combination of references still fails to provide a step of adding "a solution of a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof to form a mixture II'" (step (d)).

In light of the foregoing remarks, Applicant respectfully requests that the Office withdraw this rejection.

V. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of pending claims 1-6 and 8-22.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 16, 2004

By:_____
Carlos M. Tellez
Reg. No. 48,638

Enclosure: B. Alberts et al., *The Molecular Biology of the Cell*, Glossary at 2, 19, 20 (3rd Ed. 1983) (5 pages)